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(21) International Application Number: PCT/US97/22333 (22) International Filing Date: 5 December 1997 (05.12.97) (30) Priority Data: 60/032,105 5 December 1996 (05.12.96) US (71)(72) Applicant and Inventor: FENICHEL, Gerald [US/US]; 234 Robin Hill Road, Nashville, TN 37205 (US). (74) Agent: WHITE, John, P.; Cooper & Dunham-LLP, 1185 Avenue of the Americas, New York, NY 10036 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: THE USE OF OXANDROLONE IN THE TREATMENT OF A NEUROLOGICAL DISORDER (57) Abstract The subject invention provides a method of treating a symptom associated with a neurologic disorder in a patient which comprises administering an oxandrolone to the patient.		

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THE USE OF OXANDROLONE IN THE
TREATMENT OF A NEUROLOGICAL DISORDER

5 This application claims priority of U.S. Provisional
Application Serial No. 60/032,105, filed December 5, 1996,
the contents of which are hereby incorporated into this
application by reference. Throughout this specification,
various publications are referenced by Arabic numerals
10 within parentheses. Full citations for these references may
be found at the end of the specification immediately
preceding the claims. The disclosure of these publications
in their entireties are hereby incorporated by reference
into this specification in order to more fully describe the
15 state of the art to which this invention pertains.

Background of the Invention

20 Oxandrolone

Oxandrolone (17-methyl-17-hydroxy-2-oxa-5-androstan-3-one)
is a known compound which is commercially available. The
preparation of oxandrolone is described, *inter alia*, in U.S.
25 Patent No. 3,128,283. Oxandrolone is an anabolic steroid
synthetically derived from testosterone. Oxandrolone has a
unique chemical structure compared with other testosterone
analogs. Oxandrolone contains an oxygen rather than a
carbon atom at the 2-position within the phenanthrene
30 nucleus (1) and lacks a 4-ene function in the A-ring. The
anabolic activity of oxandrolone is approximately 6 times
greater than its androgenic activity and has been found to
be 6.3 times greater than that of methyltestosterone (1).

35 Anabolic activity refers to the ability to cause nitrogen
retention, promoting weight gain and increasing muscle
strength. Androgenic activity refers to the ability to
enhance male characteristics (i.e. secondary sex

characteristics such as facial hairs and voice changes). Because of the high ratio of anabolic to androgenic activity, oxandrolone is less likely to cause adverse cosmetic consequences in women than many testosterone
5 analogs.

Furthermore, in contrast to the majority of oral androgenic anabolic steroids (e.g. micronized testosterone, methyltestosterone, fluoxymesterone), oxandrolone undergoes
10 relatively little hepatic metabolism (2, 3).

Oxandrolone has been administered to malnourished patients with alcoholic hepatitis (4, 5). Oxandrolone has been shown to be safe even in dosages of up to 80 mg/day in patients
15 with alcoholic hepatitis (4).

The subject invention discloses the use of an oxandrolone in the treatment of a symptom associated with a neurological disorder.

Summary of the Invention

The subject invention provides a method of treating a symptom associated with a neurologic disorder in a patient
5 which comprises administering an oxandrolone to the patient.

Detailed Description of the Invention

Oxandrolone as used herein encompasses 17-methyl-17-hydroxy-2-oxa-5-androstan-3-one (both racemic mixtures and optically active enantiomers) as well as pharmaceutically acceptable esters thereof. For example, an oxandrolone product which is commercially available is the Oxandrin[®] tablet from BTG Pharmaceuticals Corp., Iselin, NJ 08830, which is 17 α -methyl-17 β -hydroxy-2-oxa-5 α -androstan-3-one. This product was used throughout the studies described herein.

Oxandrolone may be administered orally, intravenously, intramuscularly, subcutaneously, topically, intratracheally, intrathecally, intraperitoneally, rectally, vaginally or intrapleurally.

If oxandrolone is administered orally, it is administered in the form of a tablet, a pill, a liquid or a capsule.

A liquid may be administered in the form of a solution or a suspension.

The compositions produced in accordance with the invention may comprise conventional pharmaceutically acceptable diluents or carriers. Tablets, pills, liquids and capsules may include conventional excipients such as lactose, starch, cellulose derivatives, hydroxypropyl methylcellulose and magnesium stearate. Suppositories may include excipients such as waxes and glycerol. Injectable solutions will comprise sterile pyrogen-free media such as saline and may include buffering agents, stabilizing agents, solubilizing agents or preservatives. Conventional enteric coatings may also be used.

Compositions for topical administration may be in the form of creams, ointments, lotions, solutions, transdermal delivery systems, transdermal patches or gels.

A neurologic disorder as used herein encompasses any neurologic disorder as defined and described in "The Merck Manual", sixteenth edition (1992). For example, muscular dystrophy, myasthenia gravis, multiple sclerosis, Alzheimer's disease, neuropathy, and amyotrophic lateral sclerosis (Lou Gehrig's disease) are neurologic disorders.

As used herein, poliomyelitis is also a neurologic disorder.

Muscular dystrophy is a group of inherited, progressive muscle disorders of unknown etiology. Examples of muscular dystrophy are Duchenne/Becker Muscular Dystrophy (DMD) and Landouzy-Dejerine muscular dystrophy.

DMD is an inexorably progressive disease of muscle that results in severe disability by the age of 10 to 12 years and in death at about 20 years. It is inherited by X-linked inheritance and caused by disturbances at the Xp21 locus. The abnormal gene product is dystrophin, a protein that links f-actin to a transsarcolemmal dystroglycan complex whose function may be to transmit the force of contraction to the extracellular matrix. Boys with DMD have no dystrophin at birth but are asymptomatic for several years. The absence of dystrophin does not cause weakness but rather increases the vulnerability of muscle fibers to necrosis from ordinary forces. Gene-replacement therapy would be the optimal treatment but is not expected to be available in the near future. Therefore, other means are being sought to decrease the rate of muscle breakdown and to increase strength in children with DMD.

Myasthenia gravis is a disorder of neuromuscular transmission and is characterized by episodic muscle weakness, mainly in muscles innervated by cranial nerves.

Multiple sclerosis is a slowly progressive CNS disease characterized by disseminated patches of demyelination in the brain and spinal cord.

Poliomyelitis is an acute viral infection with a wide range of manifestations, including non-specific minor illness, aseptic meningitis (nonparalytic poliomyelitis), and flaccid weakness of various muscle groups (paralytic poliomyelitis).

5

Alzheimer's disease is a progressive degenerative condition with general atrophy of the brain with loss of neurons and reduced synaptic density in cerebral cortex.

10 Neuropathy is frequent among alcoholics and the malnourished. Neuropathy is also a neurocomplication in short-bowel syndromes, in diabetic patients and as a result of radiation injury. Neuropathy can also be hereditary.

15 Hereditary neuropathies are either hereditary sensory-motor neuropathies or hereditary sensory neuropathies. Examples of these neuropathies are peroneal muscular atrophy (Charcot-Marie-Tooth [CMT] disease), and neurofibromatosis. The main problem in these patients is pedal mutilation due
20 to insensitivity to pain with frequent infections and osteomyelitis.

 Amyotrophic Lateral Sclerosis (ALS) is a motor neuron disease characterized by muscle weakness and wasting due to
25 denervation, by progressive degeneration of corticospinal tracts and anterior horn cells or bulbar efferent neurons.

 Interferon as used herein encompasses any interferon, preferably beta-interferon.

30

 Corticosteroid as used herein encompasses inter alia glucocorticoids, mineralcorticoids and androgens. Examples of glucocorticoids are hydrocortisone, cortisone, corticosterone and synthetic analogs of hydrocortisone and
35 cortisone (such as cortisol, prednisolone and prednisone). Examples of mineralcorticoids are aldosterone and desoxycorticosterone. Examples of androgens are DHEA, androstenedione, testosterone and 11 β -

hydroxyandrostenedione.

The subject invention provides a method to slow down the progression of weakness in a patient suffering from muscular dystrophy such as Duchenne Muscular Dystrophy which comprises administering an oxandrolone to the patient.

The subject invention provides a method to strengthen the muscles of a patient who suffers from muscle dystrophy which comprises administering an oxandrolone to the patient.

The subject invention provides a method of treating a symptom associated with a neurologic disorder in a patient which comprises administering a therapeutically effective amount of an oxandrolone to the patient.

The subject invention also provides a use of an oxandrolone in the preparation of a composition to treat a symptom associated with a neurologic disorder.

The subject invention also provides a use of an oxandrolone in the preparation of a composition to slow down the progression of weakness in a patient suffering from muscular dystrophy.

The subject invention also provides a use of an oxandrolone in the preparation of a composition to strengthen the muscles in a patient suffering from muscle dystrophy.

The oxandrolone may be administered in conjunction with a corticosteroid, an interferon or any known anti-inflammatory agent.

The oxandrolone may also be administered in conjunction with glutamine or human growth hormone.

In a preferred embodiment of the invention, the neurologic disorder is selected from the group consisting of muscular

dystrophy, multiple sclerosis, poliomyelitis, or amyotrophic lateral sclerosis.

5 In an especially preferred embodiment, the muscular dystrophy is Duchenne muscular dystrophy.

In a preferred embodiment, the amount of oxandrolone administered is about 0.05-0.2 mg/kg/day.

10 The oxandrolone may be administered in a solid dosage form, in a liquid dosage form, in a sustained-release formulation or in a once a day formulation. The liquid dosage form may inter alia be alcohol-based or formulated with a cyclodextrin such as hydroxypropyl- β -cyclodextrin.

Example

The Example which follows is set forth to aid in understanding the invention but is not intended to, and should not be construed to, limit its scope in any way.

The Effect of Oxandrolone on Patients with Duchenne Muscular Dystrophy (DMD)10 METHODS

Patients. Ten boys were selected from Muscular Dystrophy Association Clinics. Their ages were 6 to 9 years. All showed typical phenotypes of DMD. The diagnosis was established by the absence of dystrophin staining to three dystrophin epitopes in three boys, the demonstration of deletions in the dystrophin gene at Xp21 in six, and by both techniques in one. None of the boys had been previously enrolled in another drug trial.

20 Medication. Oxandrolone was supplied by *Bio-Technology General Corp.* in tablets containing 2.5 mg of oxandrolone and the inactive ingredients: corn starch, lactose, magnesium stearate, and hydroxypropyl methylcellulose. After the initial evaluation each boy was given 0.1 mg/kg/day of oxandrolone. All study subjects took the medication daily throughout the course of the three month trial.

30 Clinical Evaluation. Manual muscle testing was performed at baseline, at one month, and at three months, by the Clinical Evaluators. Thirty four muscle groups were graded according to a grading system of the Medical Research Council that has been expanded to a 10-point scale. An average muscle score for all 34 muscles is calculated by adding all muscle scores and dividing by 34. (6, 7).

Statistical Analysis. The average muscle score is used as

the primary outcome measure because it remains linear throughout the course of disease (7), and the reliability is high from visit-to-visit and between the two clinical evaluators (8). Results are expressed as mean \pm standard error. The mean of the changes in the average muscle score for the ten boys measured at 1 and 3 months was calculated and compared to the mean of the changes in the average muscle score of the natural history controls (9) using a single group t-test.

RESULTS

Efficacy. All ten boys completed the three month study. After 3 months the mean of the changes in the average muscle score of the oxandrolone treated boys was an improvement of 0.315 ± 0.097 . The expected mean change in muscle score after 3 months from the natural history data is a loss of 0.1. The difference of 0.415 between the actual and the expected values is significant at $p < 0.01$. The mean improvement in strength of 0.315 is also significant ($p < 0.02$) even if the assumption is made that no change in strength would have occurred in the control group. Significant improvement in muscle strength (0.305 ± 0.103 ; $p < 0.02$) was also noted at the earlier time point of one month.

DISCUSSION

In this pilot study of ten DMD boys treated with 0.1 mg/kg/day of oxandrolone, strength improved over three months compared to a small deterioration in the natural history controls (9). The difference was significant at $p < 0.01$. The result is also significant assuming no deterioration in the natural history data.

The magnitude of the improvement was similar to that seen for a prednisone treated group at 6 months in an open trial (1) and at 3 months in a randomized, placebo-controlled

trial (11). The beneficial effects of prednisone last for at least three years (12). Unfortunately, prednisone has adverse effects that limit its long-term usefulness in many boys (13). Oxandrolone has not been used previously in children with neuromuscular disorders. Stanazolol, another anabolic steroid, increases muscle protein synthesis in boys with Duchenne muscular dystrophy (DMD) (14), and supraphysiologic doses of testosterone, especially combined with exercise, increase fat-free mass and muscle size in normal men (15).

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What is claimed is:

- 5 1. A method of treating a symptom associated with a neurologic disorder in a patient which comprises administering a therapeutically effective amount of an oxandrolone to the patient.
- 10 2. A method according to claim 1 wherein a corticosteroid is administered in conjunction with the oxandrolone.
- 15 3. A method according to claim 1 wherein an interferon is administered in conjunction with the oxandrolone.
- 20 4. A method according to claim 1 wherein the neurologic disorder is selected from the group consisting of muscular dystrophy, multiple sclerosis, poliomyelitis, neuropathy, and amyotrophic lateral sclerosis.
- 25 5. A method according to claim 4 wherein the muscular dystrophy is Duchenne muscular dystrophy.
- 30 6. A method according to claim 5 wherein the amount of the oxandrolone is about 0.05-0.2 mg/kg/day.
- 35 7. A method of increasing muscle strength in a patient suffering from muscular dystrophy which comprises administering a therapeutically effective amount of an oxandrolone to the patient.
8. A method of slowing down the progression of muscle weakness in a patient suffering from muscular dystrophy which comprises administering a therapeutically effective amount of an oxandrolone to the patient.
9. A method according to claims 7 or 8 wherein the muscular dystrophy is Duchenne Muscular Dystrophy.
10. A method according to claim 9 wherein the amount of the

oxandrolone is about 0.05-0.2 mg/kg/day.

- 5
11. A method according to claims 1, 7 or 8 wherein the oxandrolone is administered orally.
12. A method according to claims 1, 7 or 8 wherein the oxandrolone is administered topically.
- 10 13. A method according to claims 1, 7 or 8 wherein the oxandrolone is injected.
14. A method according to claims 1, 7 or 8 wherein the oxandrolone is in a solid dosage form.
- 15 15. A method according to claims 1, 7 or 8 wherein the oxandrolone is in a liquid dosage form.
16. A method according to claims 1, 7 or 8 wherein the oxandrolone is in a sustained-release formulation.
- 20 17. A method according to claims 1, 7 or 8, wherein the oxandrolone is 17α -methyl- 17β -hydroxy-2-oxa- 5α -androstan-3-one.
- 25

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/22333

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/56

US CL :514/170, 178

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/170, 178

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4,617,299 A (KNEPPER) 14 October 1986.	1-17
A	US 5,026,692 A (KUNO et al.) 25 June 1991.	1-17
A	US 5,183,815 A (SAARI et al.) 02 February 1993.	1-17

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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RAYMOND J. HENLEY III

Facsimile No. (703) 305-3230

Telephone No. (703) 308-1235